REMARKS

Claims 24-31 and 73-75 were pending the application. Claim 24 has been cancelled, without prejudice, claims 25, 28, and 30, have been amended, and new claims 76-82 have been added. Accordingly, upon entry of this amendment, claims 25-31 and 76-82 will be pending. For the Examiner's convenience, the pending claims are set forth in Appendix A.

Support for the amendments to the claims and the new claims may be found throughout the specification, including the originally filed claims.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claim 12 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 28 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[c]laim 28 is indefinite in the recitation "a pharmaceutical composition" because [it's] base claim 25 recites an antibody and it is unclear how the antibody would further comprises (*sic*) a pharmaceutical composition."

Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution of the application, and in no way acquiescing to the Examiner's rejection, Applicants have amended claim 28 such that it is directed to the antibody of claim 25 or 78, or an antigen binding fragment thereof, further comprising a pharmaceutically acceptable carrier. Claim 28 no longer recites the phrase "pharmaceutical composition." Accordingly, Applicants respectfully request withdrawal of the foregoing rejection under 35 U.S.C. §112, second paragraph.

Rejection of Claims 25-27, 29-31, and 73-75 Under 35 U.S.C.§ 102(b)

The Examiner has rejected claims 25-27, 29-31, and 73-75 under 35 U.S.C. §102(b) as being "anticipated by Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced

by Lu *et al* (Proc Natl Acad Sci 98:2393-2398, 2002)." In particular, the Examiner is of the opinion that

> Huang *et al* teach five antibodies BL5, F8.8, May.035, TS1/22 and TS2/6 which selectively bind to an integrin I-domain (see page 3163 under mAbs and Cell Lines, and page 3164 Figure 2 in particular). Those antibodies bind to specific epitope on the integrin aL subunit of I-domain of LFA-1 integrin (page 3164 Figure 2 in particular). Although Huang *et al* do not teach the specific antibodies bind to a modified integrin 1-domain in the open conformation, the antibodies bind to an activation specific epitope (I domain) on the integrin, the antibodies blocks an interaction between an integrins and a cognate ligand, wherein said modified I-domain of an aL subunit contains amino acid substitutions K287C/K294C or E284C/E301C and wherein modified LFA-1 I-domain contains amino acid substitutions K287C/K294C or E284C/E301C, all these limitations are considered an inherent property of the reference antibodies. As is evidenced by L[u] *et al,* that antibodies against aL I domain of LFA-1, BL5, F8.8, May.035, TS1/22 and TS2/6 bind to the open or "active" mutants K287C/K294C of aL subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu *et al* teach that BL5, F8.8, May.035, TS1/22 and TS2/6 antibodies strongly inhibited binding of both wild-type and mutant K287C/K294C of aL subunit of LFA-1 (page 2395, Table 2 in particular). Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to a modified integrin I -domain in the open conformation and binds an activation specific epitope on the integrin I-domain recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Applicants respectfully traverse the foregoing rejection under 35 U.S.C. §102(b) for the following reasons. As amended, claim 25 is directed to recombinant antibodies, or antigen binding fragments thereof, which selectively bind to a modified integrin I-domain in the open conformation. Amended claim 30 is directed to recombinant anti-LFA-1 antibodies, or antigen binding fragments thereof, which selectively bind to an LFA-1 I-domain in the open conformation. Claim 79 is directed to antibodies, or antigen binding fragments thereof, which selectively bind to a modified I-domain of an αL subunit containing amino acid substitution E284C/E301C.

For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. §102, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that Huang *et al.* fail to teach each and every limitation of the pending claims. Huang *et al.* describe the use of ***mouse anti-human monoclonal antibodies*** for research purposes, *i.e.,* to study folding during biosynthesis of different regions of the LFA-1 αL subunit, including the β propeller domain and the I domain.

Huang *et al.* do not teach or suggest the claimed ***recombinant*** antibodies. The antibodies described in Huang, *et al.* are not recombinant antibodies, *e.g.,* they were not produced or expressed by standard recombinant means. Rather, the mouse antibodies utilized by Huang *et al.* are mouse monoclonal antibodies produced from hybridomas.

Moreover, Huang *et al.* do not teach or suggest antibodies which selectively bind to modified LFA I-domain proteins ***which contain the specific amino acid substitutions E284C/E301C***, as claimed in new claim 79.

The Examiner has cited Lu *et al.*, which has a publication date after the filing date of the instant application, as evidence that some of the mouse anti-human antibodies described in Huang *et al.* bind to the open αL subunits of LFA-1 and inhibit binding of both wild-type and mutant αL subunits of LFA-1. The Examiner has not applied Lu *et al.* as anticipatory prior art. Rather, the Examiner relies on Lu *et al.* only to describe a teaching which the Examiner believes is inherent in the applied reference Huang *et al.* In view of the foregoing remarks and the amendments to the claims, Huang *et al.*, which has been cited by the Examiner as anticipatory prior art, does not teach or suggest each and every limitation of the claimed invention and therefore does not anticipate the claimed invention. Accordingly, the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. §102(b).

Rejection of Claims 25-27, 29-31, and 73-75 Under 35 U.S.C.§ 103(a)

The Examiner has rejected claims 25-27, 29-31 and 73-75 under 35 U.S.C. §103(a) as being "unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) in view of Owens *et al* (1994)." In particular the Examiner is of the opinion that

> [t]he claimed invention differs from the reference teachings only by the recitation of an antigen binding fragment. Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment, or a F(ab')2 fragment. Owens *et al* further teach antibody fragments are the reagents of choice for some clinical applications (see the entire document). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the antibodies taught by Huang *et al* as Fab and F(ab')2 fragments taught by the Owens *et al.* One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants respectfully traverse the foregoing 35 U.S.C. §103 rejection for the following reasons.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP 706.02(j).

Applying this standard to the references cited by the Examiner, it is clear that the prior art references do not teach or suggest all of the claim limitations for the reasons stated above. In particular, the cited references, in combination, do not teach or suggest all of the claim limitations of the claims, as amended. Specifically, the primary reference of Huang *et al.* fails to teach or suggest the claimed ***recombinant antibodies***. Moreover, Huang *et al.* do not teach or suggest antibodies which selectively bind to modified LFA I-domain proteins which contain amino acid substitutions E284C/E301C. The secondary reference of Owens *et al.* fails to cure the deficiencies in the teachings of the Huang *et al.* reference as it does not describe recombinant antibodies which selectively bind to a modified integrin I-domain in the open conformation.

In view of the foregoing, Applicants respectfully submit that the combination of Huang *et al.* and Owens *et al.* fail to teach or suggest Applicants' invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the instant 35 U.S.C. §103 rejection.

Rejection of Claim 28 Under 35 U.S.C.§ 103(a)

The Examiner has rejected claim 28 under 35 U.S.C. §103(a) as "being obvious over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) in view of U.S Patent No. 6,413,963." In particular, the Examiner is of the opinion that

> [t]he teachings of Huang *et al* and Lu *et al* cited as an evidentiary reference have been discussed, supra. The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition and a pharmaceutically acceptable carrier. The '963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The "963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular). It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antibodies taught by Huang *et al* reference in a pharmaceutical compositions in a pharmaceutically acceptable carrier taught by the "963 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by "963 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

As set forth above, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP 706.02(j).

Applying this standard to the references cited by the Examiner, it is clear that the prior art references do not teach or suggest all of the claim limitations for the reasons stated above. In particular, the cited references, in combination, do not teach or suggest all of the claim limitations of the claims, as amended. Specifically, the primary reference of Huang *et al.* fails to teach or suggest the claimed ***recombinant antibodies***. Moreover, Huang *et al.* do not teach or

suggest antibodies which selectively bind to modified LFA I-domain proteins which contain amino acid substitutions E284C/E301C. The secondary reference of U.S Patent No. 6,413,963 fails to cure the deficiencies in the teachings of the Huang *et al.* reference as it does not describe recombinant antibodies which selectively bind to a modified integrin I-domain in the open conformation.

In view of the foregoing, Applicants respectfully submit that the combination of Huang *et al.* and U.S Patent No. 6,413,963 fail to teach or suggest Applicants' invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the instant 35 U.S.C. §103 rejection.

CONCLUSION

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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Dated: **February 14, 2003**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel claim 24, without prejudice, and amend claims 25, 28, and 30, as follows:

25. **(Amended)** A~~n~~ recombinant antibody, or an antigen binding fragment thereof, which selectively binds to a modified integrin I-domain in the open conformation.

28. **(Amended)** The antibody of claim 25 or 78, or an antigen binding fragment thereof, further comprising ~~a pharmaceutical composition and~~ a pharmaceutically acceptable carrier.

30. **(Amended)** A~~n~~ recombinant anti-LFA-1 antibody, or an antigen binding fragment thereof, which selectively binds to an LFA-1 I-domain in the open conformation.

Please add new claims 76-82 as follows:

76. **(New)** The antibody of claim 25 or 30, or an antigen binding fragment thereof, wherein said antibody is a human antibody.

77. **(New)** The antibody of claim 25 or 30, or an antigen binding fragment thereof, wherein said antibody is a humanized antibody.

78. **(New)** The antibody of claim 25 or 30, or an antigen binding fragment thereof, wherein said antibody is a chimeric antibody.

79. **(New)** An antibody, or an antigen binding fragment thereof, which selectively binds to a modified I-domain of an αL subunit containing amino acid substitution E284C/E301C.

80. **(New)** The antibody of claim 25, wherein said antibody, or antigen binding fragment thereof, is identified by screening a phage display library with a modified integrin polypeptide, and isolating said antibody, or antigen binding fragment thereof.

81. **(New)** The antibody of claim 79, wherein said modified integrin polypeptide is stabilized in the open conformation.

82. **(New)** The antibody of any one of claims 25, 30, or 79, wherein said antibody is a monoclonal antibody.

APPENDIX A

25. A recombinant antibody, or an antigen binding fragment thereof, which selectively binds to a modified integrin I-domain in the open conformation.

26. The antibody of claim 25, or an antigen binding fragment thereof, which binds to an activation specific epitope on the integrin I-domain.

27. The antibody of claim 25, or an antigen binding fragment thereof, which blocks an interaction between an integrin and a cognate ligand.

28. The antibody of claim 25, or an antigen binding fragment thereof, further comprising a pharmaceutically acceptable carrier.

29. The antibody of claim 25, or an antigen binding fragment thereof, wherein said antibody is an anti-LFA-1 antibody.

30. A recombinant anti-LFA-1 antibody, or an antigen binding fragment thereof, which selectively binds to an LFA-1 I-domain in the open conformation.

31. The anti-LFA-1 antibody of claim 30, or an antigen binding fragment thereof, wherein said anti-LFA-1 antibody, or an antigen binding fragment thereof, selectively binds to a modified LFA-1 I-domain.

73. The antibody of one of claim 25, or an antigen binding fragment thereof, wherein said antibody, or antigen binding fragment thereof, selectively binds to a modified I-domain of an αL subunit.

74. The antibody of claim 73, or an antigen binding fragment thereof, wherein said modified I-domain of an αL subunit contains amino acid substitutions K287C/K294C or E284C/E301C.

75. The anti-LFA-1 antibody of claim 31, or an antigen binding fragment thereof, wherein said anti-LFA-1 antibody, or an antigen binding fragment thereof selectively binds to a modified LFA-1 I-domain, wherein said modified LFA-1 I-domain contains amino acid substitutions K287C/K294C or E284C/E301C.

76. The antibody of claim 25 or 30, or an antigen binding fragment thereof, wherein said antibody is a human antibody.

77. The antibody of claim 25 or 30, or an antigen binding fragment thereof, wherein said antibody is a humanized antibody.

78. The antibody of claim 25 or 30, or an antigen binding fragment thereof, wherein said antibody is a chimeric antibody.

79. An antibody, or an antigen binding fragment thereof, which selectively binds to a modified I-domain of an αL subunit containing amino acid substitution E284C/E301C.

80. The antibody of claim 25, wherein said antibody, or antigen binding fragment thereof, is identified by screening a phage display library with a modified integrin polypeptide, and isolating said antibody, or antigen binding fragment thereof.

81. The antibody of claim 79, wherein said modified integrin polypeptide is stabilized in the open conformation.

82. The antibody of any one of claims 25, 30, or 79, wherein said antibody is a monoclonal antibody.